impulses generated in this way be amplified by neurogenic mechanisms elicited by nerve compression which is secondary to the cervical spine disease.

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Tacrolimus in the treatment of severe chronic idiopathic urticaria: An open-label prospective study

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We report the result of a pilot study of low-dose tacrolimus for the treatment of patients with severe chronic idiopathic urticaria (CIU). Nineteen patients with severe CIU were treated with tacrolimus for 12 weeks. Two patients dropped out after 1 week of treatment because of side effects. Following 3 months of treatment, 12 of 17 patients (70.5%) had a clinical response to tacrolimus. In 9 patients, the urticaria had been improved significantly (urticarial score 0-1), enabling them to discontinue antihistamines and, in the case of two patients, corticosteroids. The remaining 3 patients had moderate improvement (urticarial score 2). Three months after the discontinuation of tacrolimus, 3 of 10 responders had a complete resolution of their urticaria (urticarial score 0), 3 had mild deterioration (urticarial score 1-2) controllable by antihistamines alone, and 4 patients had a full relapse (urticarial score 3). Our preliminary results suggest tacrolimus as a treatment option for patients with severe CIU. (J Am Acad Dermatol 2005;52:145-8.)

While several treatment options have been proposed for the treatment of severe chronic idiopathic urticaria (CIU), most published studies support the use of cyclosporin A (CSA).[1-3] However, this treatment induces short-term full remission in two thirds of patients and a long-term improvement is achieved in only a quarter of patients.[2-3] Additionally some patients suffer from side effects which prevent them from using this drug. For this reason it was important to look for an alternative treatment for severe CIU.

Tacrolimus (FK506; Prograf, Killorgin, Ireland) is a macrolide lactone, which was isolated in 1984 from streptomyces tsukubaensis. Similar to CSA, it binds to intracellular proteins and thereby interferes with the signal transduction from cell surface receptors to the nucleus of T-lymphocytes, preventing transcription of lymphokine genes involved in T-cell activation and the formation of interleukin-2.[4] Tacrolimus is a potent inhibitor of histamine release from basophiles activated by antigen and anti-IgE, as well as an inhibitor of histamine release and de novo synthesized inflammatory mediators (sulfidpeptide leukotriene C4 and prostaglandin D2) from mast cells.[5,6] Therefore, we decided to investigate the effect of tacrolimus on clinical features in patients with severe CIU.

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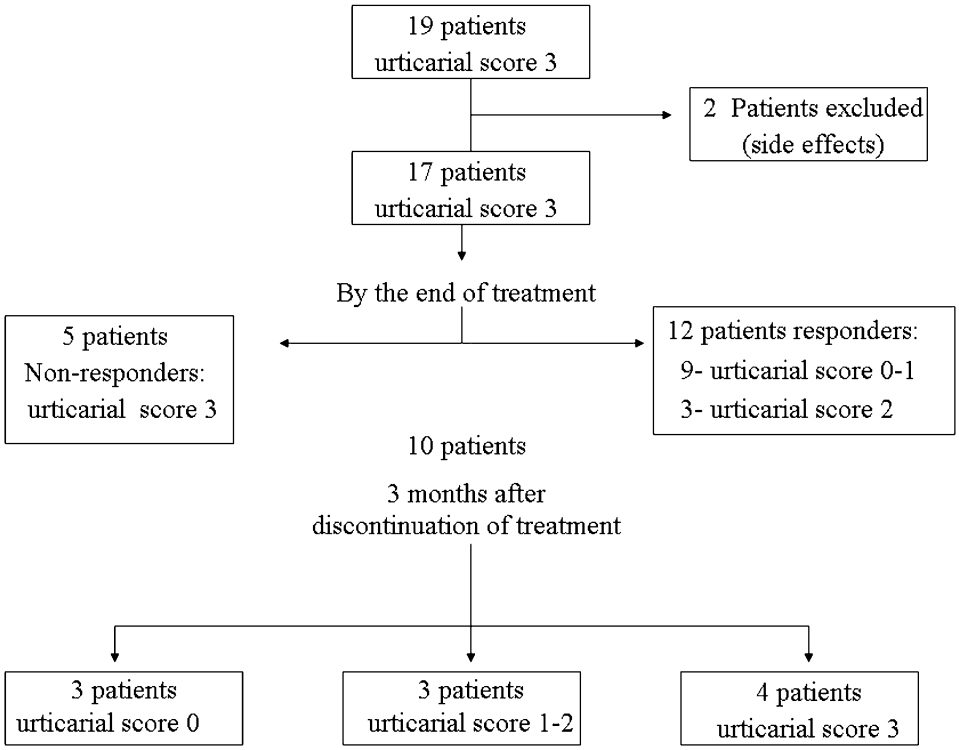

Fig 1. Clinical outcome of tacrolimus therapy.

METHODS

We conducted an open-labeled prospective study with 19 patients (mean age 33 ± 11.5 years, 14 women and 5 men) with severe unremitting disease lasting more than 12 months (mean 4.7 ± 3 years). The patients were recruited from the allergy clinic at the Bnai Zion Medical Center from January 2003 to January 2004. All patients responded poorly to H_1 antihistamines, given alone, or in combination with H_2 antihistamines. Two patients required daily prednisolone (5-10 mg daily) for 6 months before their recruitment into the study. The other 17 received 2 to 3 short courses of prednisolone in the 6 months preceding the initiation of the trial.

All patients were diagnosed as suffering from CIU following the exclusion of pure physical urticaria, infectious diseases, and food or food additive hypersensitivity. Exclusion criteria were: pregnancy, known malignant disease, a history of epilepsy or neurological diseases, hypertension, renal or liver disease, ischemic heart disease, and diabetes mellitus.

The out-patient study group was treated daily with tacrolimus (FK 506; Fujisawa Ireland Ltd, Killorgin, Ireland). Tacrolimus was initially given as a daily dose of 0.05 mg/kg to 0.07 mg/kg administered orally twice a day for 4 weeks followed by 6 weeks of 0.025 mg/kg/day to 0.035 mg/kg /day. Subsequently, the drug was continued for an additional 2 weeks at a dose of 1 mg per day and then discontinued (total treatment period of 12 weeks). The initial dose was chosen in accordance with our previous clinical experience demonstrating clinical improvement with minimal side-effects. All patients were examined biweekly for blood, electrocardiography, blood counts, serum creatinine, liver enzymes, and electrolytes for the first 6 weeks, and thereafter as applicable.

Patients recorded their urticaria symptoms daily, rated on a 4-point scale, as detailed previously by Breneman et al[7]: number of lesions, number of separate episodes, average size of lesions, and average duration of lesions and pruritus. Table I details the scoring system: 0 = no symptoms, 1 = mild urticaria (1-4 points), 2 = moderate urticaria (5-9 points), 3 = severe urticaria (≥10 points). All patients were scored as having severe urticaria (score 3) within the 6-month period preceding the commencement of the tacrolimus study protocol. Every 2 weeks, at each follow-up visit, the physicians rated the urticaria symptoms using the same scoring system. Response was defined as an improvement in the patient's urticarial score.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Bnai Zion Medical Center Human Research Committee. All

patients gave their informed consent after receiving a full explanation of the protocol.

RESULTS

During the first week of treatment, tacrolimus was discontinued in 2 out of the 19 patients because of severe abdominal pain, diarrhea, and headache. Within 5 to 10 days of initiating tacrolimus therapy, improvement was noted in 12 out of the 17 remaining patients (responders).

By the end of treatment, improvement was noted in 9 out of the 12 responders as evident by their 0-1 score on the urticaria scale. Additionally, the 9 patients no longer required antihistamines and 2 were even able to discontinue corticosteroids. The remaining 3 responders had moderate improvement (urticarial score 2). Of note all patients who responded to the tacrolimus also reported a decrease in work absenteeism and increased attendance of social events. Side-effects among these patients were mild and self limited: mild diarrhea (n = 6), abdominal pain (n = 2), tingling of the fingers, feet, or lips (n = 2).

Five patients were categorized as non-responders as no benefit was observed following 4 weeks of therapy. In these non-responders therapy was then stopped. Ten out of the 12 responders were followed for an additional 3 months after the discontinuation of tacrolimus. Three of them had a complete resolution of their urticaria (urticarial score 0), 3 had mild deterioration (urticarial score 1-2) controllable by antihistamines alone, and 4 patients had a full relapse (urticarial score 3). Results are summarized in Fig 1.

Table I. Patient's and investigator's rating scale of symptom severity*

Daily events	Points
No. of lesions	
0	0
1-10	1
11-20	2
>20	3
No. of separate episodes	
0	0
1	1
2-3	2
>3	3
Average size of lesion (inches)	
0	0
<0.5	1
0.5-1	2
>1	3
Average duration of lesions (h)	
None	0
Up to 4	1
4-12	2
>12	3
Pruritus	
None	0
Mild	1
Moderate	2
Severe	3

Adapted from Breneman et al.[7]
*0 = No symptoms; 1 = mild urticaria (1-4 points); 2 = moderate urticaria (5-9 points); 3 = severe urticaria (≥10 points).

DISCUSSION

In conclusion, 12/17 (70.5%) had a clinical response to tacrolimus, with 9 patients experiencing a significant improvement. This response was still apparent in 6 of 10 patients 3 months after tacrolimus discontinuation. It is of note that one of our patients who experienced a full remission had previously not shown a response to a low dose of CSA (3 mg/kg/day) taken for 3 weeks. The most common side effect among our patients was transient gastrointestinal complaints (ie, diarrhea and abdominal pain). Two patients discontinued tacrolimus secondary to severe diarrhea and headaches. We did not encounter infections, tremor, or abnormal kidney function side effects that are frequently reported among patients receiving higher doses of tacrolimus. The observed beneficial effect of tacrolimus is most likely related in part to the assumption that CIU is a T-cell mediated disorder, particularly since most of cellular infiltrate in CIU is composed of CD4+ T cells.[8] Additionally, we have demonstrated the over-expression of CD_{40L} on activated T cells from such patients.[9]

Thus, the mechanism by which tacrolimus is effective in the treatment of CIU may be related to its inhibitory effects on activated T cells, which may influence mast cell degranulation. It has also been shown that tacrolimus can directly inhibit histamine release from basophiles and mast cells.

Although this study was conducted on a small group of patients, we provide first clinical data that tacrolimus may be a reasonable treatment for severe CIU. Similarly to CSA treatment, approximately 3 out of 4 patients respond to tacrolimus. Furthermore, as for CSA treatment, it appears that some patients require a prolonged treatment for CIU, in order to maintain a clinical response. Taken together, these data may suggest that tacrolimus could potentially ameliorate the clinical course of patients with severe disease that do not respond to CSA treatment.

The major shortcoming of the study is that it was not a double-blind, placebo randomized controlled study. An additional limitation is the relatively small

sample size. In order to establish tacrolimus as an alternative treatment, the optimal dose and duration of therapy in CIU still needs to be investigated in double-blind, placebo-controlled studies.

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